Message

From: Anastasia Coots [Anastasia_Coots@cargill.com]
Sent: 3/24/2018 5:42:15 AM
To: Beck, Nancy [Beck.Nancy@epa.gov]; Morris, Jeff [Morris.Jeff@epa.gov]
CC: Bauer, Jeff [Bauer.Jeff@epa.gov]
Subject: RE: Sustainable Futures TME/PMN Needs Your Attention

Thanks Nancy,

I did receive a call from the team and there is definitely follow-up questions and concerns that we have in regards to the direction of the risk assessments. I have asked the team to fax us a copy of the newest risk assessment with the engineering report this time for us to review their refined new calculations and all the references they were using as the basis of their concerns. Just from the phone call there still seems to be contradiction to the team's supporting arguments to their continued concern for health hazard risk after adjustments to the assessment and review of the analogue 422/414 data. In addition, there seems to be an added potential restriction based on inhalation because the risk assessors chose not to evaluate for risk? We did provide additional referenced acute and chronic inhalation data for analogues this has been previously found by EPA for the category of polyol esters under HPV assessments not to be a concern.

We are still looking to resolve this through providing all of the best available references and ask that all existing supporting data is considered prior to any discussion of a potential SNUR.

Based on the Call from the Team:
It seems with the correction in exposure risk calculations the chemical passes the original established risk PODs of 300 mg/kg/day for blood effects and the alternate POD established for developmental tox based on 100 mg/kg/day. Based on my calculations on the numbers they provided during the call the chemical would have an MOE 5-7x greater than the bench mark of 100 from original risk calculations.

However, for the Team indicated that for the second assessment they adjusted the POD for development tox in the risk calculation to 10 mg/kg/day. There was no question to the original established POD of 100 mg/kg/day for development tox data of the fatty acid, we were and still are opposed to the use of a direct dose study of the fatty acid when there is more appropriate surrogate OECD 422/414 studies available. It is unclear why this was adjusted or lower from the first assessment.

In addition, the explanation of the rejection of existing analogue OECD 422/414 data (which is a constituent of this mixed tetraester) seems to be based on two incomplete theories.

1) Assessors described their concern that data on the analogue ester of the branched fatty acid is insufficient to represent the other constituents of the mixed tetraester which is a combination of branched and linear fatty acid due to biodegradation and environmental fate data which indicates the analogue degrades or hydrolyzes slower than the remaining constituents of the mixed tetraesters.
    a. In this scenario, it is inappropriate to try to correlate a 301 F 28-day biodegradation study or hydrolysis modeling of poorly water soluble materials based in aquatic environments with pH of 7-8 as indication of potential express rates of enzymatic hydrolysis in mammalian gastrointestinal tracts (GIT). We do not contend that there is steric hinderance that can occur, however, there is literature available on studies of enzymatic hydrolysis of fully esterified alcohols see 2b below.
2) Assessors made reference to concern for developmental tox based on the fatty acid due to predicted hydrolysis in mammals by expressed esterases based on references on triglycerides and glycerol esters. It was not clear if this was based on referenced studies that showed same esterase after dermal absorption as the assessor kept interchanging the use of the term absorption as in the gastrointestinal tract (GIT) and dermal absorption.
    a. We are not aware of any correlation to studies from the dermal absorption of polyol tetraesters and predicted rates of enzymatic hydrolysis in the GIT. All of the concerns raised are still based on the developmental tox data available for oral ingestions of the starting fatty acid as predictive measures of the risk from enzymatic hydrolysis after dermal absorption of insoluble, fully esterfied tetraesters with a MW range of >500.

b. We do not disagree with the potential of hydrolysis by esterases in the GIT but the reference to the rate of hydrolysis and absorption based on references for vegetable oils, triglycerides, or glycerol esters is not appropriate for polyol esters with more than 3 ester groups, studies have shown lower rates of enzymatic hydrolysis in the GIT for compounds with more than 3 ester groups. We would ask the assessors to review Mattsson and Volpenhein 1972a-c, see below references. In vitro hydrolysis rate of a fully linear polyol tetraester was about 2000 times slower in comparison to glycerol esters (Mattson and Volpenhein, 1972a, b). Moreover in vivo studies in rats demonstrated the incomplete absorption of the compounds containing more than three ester groups. This decrease became more pronounced as the number of ester groups increased (Mattson and Volpenhein, 1972c). Based on this, it can be assumed that, on the one hand, the polyol tetraesters regardless of branching is not considered to be rapidly hydrolyzed in the GIT by esterases and, on the other hand, absorption of the whole substance can be considered to be very low.

Based on the above, the available 422/414 analogue data is still expected to provide the highest concentration potential for the fatty acid in question that may be present from enzymatic hydrolysis of the mixed tetraesters (worst case) based on mole fraction of the fatty acid.

If this is still not sufficient to address the concerns from the risk assessors, I did find an additional OECD 414 Study (oral) from 1996 referenced in a REACH registration for C16-C18 Alkyl esters of the fatty acid of concern which can be used as an additional supporting analogue specifically to address concerns raised by the risk assessor surrounding the steric hinderance concerns of the analogue and potential lower bioavailability of the fatty acid due to slower hydrolysis. As the C16-C18 alkyl ester is a linear fatty alcohol ester with the branched fatty acid in question, it would be expected to have a much higher rate of expected enzymatic hydrolysis than our chemical with little expected steric hinderance. I will call Jeff Bauer with details on specific identity on Monday.

The additional supporting analogue also has similar physio/chemical properties to our chemical including low water solubility and is readily biodegradable (>90% in 28 days) or considered rapidly degradable. Even though the supporting analogue has lower MW range, the low solubility and log Pow values (measured: 5.28; calculated: >10) indicate absorption in the GIT is expected to be limited and will go through similar enzymatic hydrolysis. In the additional OECD 414 study, the fatty acid of concern was also dosed at 600 mg acid/kg bw/day as a positive control group with the aim of inducing clear maternal and developmental toxicity (including signs of teratogenicity), but no excessive maternal toxicity. Doses were chosen for the alkyl esters in the main study: 600 mg/kg bw/day – as the expected NOAEL, 1000 mg/kg bw/day – as the intermediate dose level and 1500 mg/kg bw/day – at this dose about 600 mg of the fatty acid/kg bw/day theoretically released by ester. The study concluded a NOAEL for the alkyl esters of 1500 mg/kg bw/day for both maternal and developmental toxicity.

Due to broad use of these type of esters in cosmetics, I may be able to find additional esters with the fatty acid of concern that have data available. I would hope that the number of studies and reference documentation that has already been provided would be sufficient to make a weight of evidence decision at this point. All data found to date would suggest an expected NOAEL of >1000 mg/kg/day for developmental tox.

Additional References:

Mattson F.H. and Nolen G.A. (1972): Absorbability by rats of compounds containing from one to eight ester groups. J Nutrition, 102: 1171-1176.

Mattson F.H. and Volpenhein R.A., (1972a): Hydrolysis of fully esterified alcohols containing from one to eight hydroxyl groups by the lipolytic enzymes of rat pancreatic juice. J Lip Res 13, 325-328

Mattson F.H. and Volpenhein R.A., (1972b): Digestion in vitro of erythritol esters by rat pancreatic juice enzymes. J Lip Res 13, 777-782

Mattson F.H. and Volpenhein R.A., (1972c): Rate and extent of absorption of the fatty acids of fully esterified glycerol, erythritol, xylitol, and sucrose as measured in thoracic duct cannulated rats. J Nutr 102, 1177-1180

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From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, March 22, 2018 3:41 PM
To: Anastasia Coots <Anastasia_Coots@cargill.com>; Morris, Jeff <Morris.Jeff@epa.gov>
Subject: RE: Sustainable Futures TME/PMN Needs Your Attention

Hi Anastasia,
I wanted to let you know I received a briefing on this today and the case manager should be getting back to you shortly. Please let me know if you have any follow-up questions after that.

Regards,
Nancy

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From: Anastasia Coots [mailto:Anastasia_Coots@cargill.com]
Sent: Friday, March 9, 2018 11:39 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>
Subject: RE: Sustainable Futures TME/PMN Needs Your Attention

Thanks Nancy,

I did receive a call yesterday from the TME product manager who indicated the risk assessors were re-evaluating, but I did find one point from my note that I was incorrect on below and just wanted to provide to you and Jeff in case this indicates a different issue in the Risk Calculations.

On Item a) below I indicated that the risk assessor had used 100% dermal absorption. That was an incorrect statement that I had based on trying to back calculate in our P2 assessment to try to match the risk assessors MOE. Which could only be achieved by plugging 100% absorption into our model. However, in review of the actual Risk Calculations received by fax the parameters used in the Risk Calculations for the Worker Risk were the following:

- Potential Dose Rate (worst case from engineering report): 1.1 E+4 mg/day over 1 day/year servicing equipment
- Exposure Route Absorption Adj: 15% (indicating 1650 mg/day is assumed absorbed dermally)
    - I did not receive an engineering report, but I have not been able to recreate any scenario for which the Potential Dose Rate would be 11,000 mg/day for a 1 day per year task, without a full body immersion scenario or setting rate application to 365 days. Using the 11,000 mg/day in the chronic risk model, the model becomes a "forced failure" where any NOAEL entered at < 2000 mg/kg/day even at the stated 15% absorption rate will fail. When 100% absorption is assumed it is indicated that a NOAEL would have to be greater than 15,000 mg/kg/day.
    - Do we need to include partial or full body immersion scenerios for dermal absorption in our P2 considerations in order to predict EPA's potential Risk Calculation outcomes? This will be helpful to know moving forward.

We do still believe there is evidence that the chemical is not likely to penetrate skin based on high MW (>500 g/mol), high Pow, and low solubility and that using a full body immersion or partial body immersion on materials that can show lower absorption potential to test the upper limit of the model would set a higher risk factor obligation to materials with lower exposure risk potential.

It would be very valuable to have examples that have been recently used by EPA's risk assessors for Highest/Worst Case Dose scenerios for Dermal in the guidance or as a separate tool that would allow Sustainable Futures participates to run a check on their P2 for predictability of EPA's Risk Calculation outcome.

Thanks again for your time and attention to these specific issues.

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From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, March 8, 2018 6:18 AM
To: Anastasia Coots <Anastasia_Coots@cargill.com>; Morris, Jeff <Morris.Jeff@epa.gov>
Subject: RE: Sustainable Futures TME/PMN Needs Your Attention

Anastasia,
Thank you for your note. We will look into this and get back to you.

Regards,
Nancy

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From: Anastasia Coots [mailto:Anastasia_Coots@cargill.com]
Sent: Thursday, March 8, 2018 4:56 AM
To: Morris, Jeff <Morris.Jeff@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Sustainable Futures TME/PMN Needs Your Attention
Importance: High

Note: The following communication does not include confidential business information. Details regarding specific chemical identity and TME/PMN reference numbers are purposefully excluded.

Hello Jeff and Nancy,

I know from the Lynn Bergeson and the New Chemicals Coalition (NCC) that you have requested specific examples of issues or feedback with the Sustainable Futures program. We currently have a TME/PMN Sustainable Future submission that went through Focus Meeting the second week of February. The chemical fits into the Polyol Esters Category previously reviewed by EPA HPV Challenge Program in 2010 and as a category of chemicals for safe use in cosmetics as part of the Cosmetic Ingredient Review program in 2012. The initial response was a Denial based on the Human Health Assessment indicating Human Health Risk for dermal exposure based on indication of 1) blood and thyroid effects with NOAEL of 300 mg/kg/day in an oral repeat dose study available for an analogue, 2) an LOAEL of 100 mg/kg/day for developmental toxicity for one of the reactants used, and 3) skin and eye irritation based on statements in SDS. Concluding recommendations for a SNUR to address mitigation through use of PPE of gloves and safety glasses in addition to testing requirements (OECD 422 study).

We were informed of the initial response a couple of weeks ago and I was trying to get concerns from the risk assessment addressed through the PMN product manager before a final denial of the TME. However, I was informed by a phone call yesterday by the TME

product manager that she was unaware of any of our on-going communications with the PMN product manager and you have already reviewed the original assessment supporting a denial.

The following is a list of specific examples that are making the Sustainable Futures program ineffective and/or need improved upon. In addition, we would still like to see our current TME/PMN issue resolved.

General Process

1) The filing of the TME/PMN jointly under the Sustainable Futures program is intended to make the review more efficient. It was not made clear to me that there were 2 separate Product Managers handling the TME and PMN separately and that I needed to address the issue of the risk assessment after the focus meeting with both managers separately.
2) We were contacted by an assigned manager to our PMN who had not reviewed our PMN and was not prepared to discuss the issue; indicated that the risk assessor had not taken into account the additional information we included in the P2 assessment; and initially just didn't seem to understand the chemistry based on comments regarding the nomenclature for esters.
3) There is a definite lack of timely communication and/or internal communication that would allow us to address issues or concerns raised by a risk assessor before the assessment gets to you for denial of a TME.
4) Specific to this TME/PMN, we had included additional information with the P2 that should have mitigated or addressed the risk assessors findings:

    a) chemical is not likely to penetrate skin based on high MW (>500 g/mol), high Pow, and low solubility, which was acknowledged in the summary by assessor as "dermal absorption is nil or poor". However, risk assessor based the risk modeling on 100% dermal absorption to derive the MOE and has based all Human Health Risk recommendations based on exposure risk through dermal absorption.

    b) The risk assessor references oral repeat tox study based on an analog indicating concern for increased blood clotting time, increased neutrophils, decreased red blood cells, increased platelets, decreased serum potassium and phosphorous, vacuolated lung macrophages, and thyroid hypertrophy and assigned a NOAEL of 300 mg/kg/day for use in modeling to derive the MOE. The study was originally concluded by study directors for the report as meeting a NOAEL of 1000 mg/kg/day based on the effects observed and indicated above where not considered significant due to lack of correlative findings or not considered adverse based on the minimal to mild severity. Study findings have been previously reviewed by other regulatory agencies and used as analogue data as supporting low or no concern findings. Additionally, when taken into account additional repeat tox studies for analogues including 422/414 studies that are available with NOAEL for hematological and systemic effects concluded no observed adverse effects for highest doses tested 1000 mg/kg/day.

    c) the reactant which is driving concerns for developmental tox with the NOAEL of 100 mg/kg/day is in fact fully reacted and any excess is removed through the process. Residuals are specified to be maintained below 0.03%. The new chemical under this submission is specific to the esters from the reaction. Any presence of the reactant greater than 0.1% is required by OSHA HazCom and the Globally Harmonized System for classification and labeling to be treated as a separate component driving hazard classification of a mixture. The reactant is included on the TSCA inventory without a SNUR. Any testing required by EPA would be with the chemical as manufactured under conditions included in the TME/PMN and would not address any concerns the risk assessor would have for subsequent manufacturers who had higher residual content of unreacted reactant. Additional 422/414 studies for analogues based on the esters with the reactant are available and endpoint data was used as our bases for weight of evidence determination of NOAEL of 1000 mg/kg/day for systemic, maternal, and developmental toxicity as summarized in our P2 assessment. A full OECD 422 study report has been published by Japan's Food and Drug Safety Center which I offered to the PMN product manager to have translated and uploaded 2 weeks ago and he said to hold off because there was indication that it was already available.

    d) Statements in SDS referenced by risk assessor as indicating concerns for skin and eye irritation which triggered a Human Health Risk finding included: "may cause minimal irritation or no effect" and "based on similar substances may be slightly irritating to eyes or skin, but not sufficient for classification" is based on valid available studies for analogues meeting OECD 404/405, Draize or similar accepted methods which results were reported for similar substance as causing slight or minimal irritation indicated by temporary redness, fully reversible within study guidelines which did not meet criteria for classification as an irritant under any current regulatory criteria (FIFRA, CPSIA/FHSA, etc). Repeat dose dermal studies for analogues indicated minimal irritation, redness, drying or flaking of skin for the category of chemicals, which when evaluated for use in cosmetics also did not indicate concern for safe use in leave-on personal care and cosmetic products. As summarized in our P2 assessment, human data is

also available for use in cosmetics including use in eyeliners. Industrial uses do not indicate potential for intended repeat or prolonged contact. However, information is provided in the SDS for recognition of symptoms. In our SDS we include in Section 11. Symptoms related to physical, chemical, and toxicological characteristics: "Repeated or prolonged skin contact may cause drying, reddening, itching or cracking. Eye contact may cause temporary redness, tearing or blurred vision." All of this information was included in our TME/PMN files, however, the risk assessor concluded that the "risk to eye and skin irritation were not quantified due to lack of a suitable POD". Triggering a human health risk requiring mitigation through use of PPE. This is very difficult to accept that this was their conclusion from what was provided.

e) In the P2 assessment as part of the TME/PMN files, we included additional studies and supporting references that can be taken into consideration for weight of evidence supporting conclusions of not likely to be a human health risk

- including references for already available additional repeat toxicity studies by oral, dermal, and inhalation routes. Available OECD 422, 414 and tox studies for analogue/ester with reactant of concern which all report NOAELs for systemic, maternal, and developmental toxicity to be greater than or equal to highest doses tested, 1000 mg/kg/day. It is unclear what additional animal testing of the new chemical according to OECD 422 will provide that is not already available from existing studies with analogue or similar ester of concern.
- the attachment of EPA's 2010 HPV Screen Level Hazard Assessment for the Chemical Category which indicated that based on the review of studies available at that time in 2010 concluded no data gaps were identified.
- a 2012 Cosmetic Ingredient Review for Safe Use of the Chemical Category by an expert panel which also concluded that the chemical category including analog which triggered concern by the EPA risk assessor was determined unlikely to penetrate the skin and to be safe for the existing identified uses in leave-on personal care and cosmetic products as indicated. Specifically esters based on the reactant of concern is used as a skin conditioning agent at concentrations of up to 40% in existing consumer products regulated by FDA.

I am a strong supporter of the Sustainable Futures Program and have been working with our development team to try to address all potential foreseeable risks when developing new chemicals and provide as much readily available information as part of our submissions. However, if this information is not being used as part of the hazard assessments completed by risk assessors and/or if we are not given the opportunity address concerns raised by the risk assessor prior to final denial of the TME, then the Sustainable Futures Program will continue to be an ineffective program for making the review process more efficient.

I hope these examples help and hope to get some relief or direction on how we can provide the information that is needed.

Thank you for your time,

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